Mapping the first stages of mesoderm commitment during differentiation of human embryonic stem cells.

Journal: Proc Natl Acad Sci U S A

Publication Year: 2010

Authors: Denis Evseenko, Yuhua Zhu, Katja Schenke-Layland, Jeffrey Kuo, Brooke Latour, Shundi Ge, Jessica Scholes, Gautam Dravid, Xinmin Li, W Robb MacLellan, Gay M Crooks

PubMed link: 20643952

Funding Grants: Regulated Expansion of Lympho-hematopoietic Stem and Progenitor Cells from Human Embryonic Stem Cells (hESC), Training Grant 1

Public Summary:
During early development, human embryonic stem cells can follow three distinct developmental pathways to form the primary germ cell layers: the mesoderm, the ectoderm and the endoderm. These three germ cell layers then become all the tissues in the human body. In this study, Dr Evseenko, Dr Crooks and colleagues studied human embryonic stem cells that followed the mesoderm pathway, which gives rise to blood cells, blood vessels, cardiac cells, muscle, cartilage, bone and fat. The investigators placed human embryonic stem cells into culture and, after three or four days, found a small subset of the cells that had lost a key cell surface marker characteristic of the pluripotent state and had gained a new marker that is a hallmark of mesodermal cells. Because the two markers are displayed on the cell surface, specific antibodies could be used to isolate the “human embryonic mesodermal progenitors” (hEMP cells) from the other cells in culture. The hEMP cells mark the very first stage of differentiation of human embryonic stem cells as they enter the mesoderm developmental pathway that leads to production of blood, heart muscle, blood vessels and bone. The researchers studied the hEMP cells using specialized culture systems to test what kind of tissues they produce and using gene arrays to understand how closely hEMP cells relate to embryonic stem cells. The knowledge of how to isolate these hEMPs, allows researchers to remove the original pluripotent stem cells and thus reduces the risk of teratoma formation after transplantation. This discovery will allow scientists to study the earliest events of tissue differentiation from pluripotent stem cells and offers a safer and more controlled method for engineering tissue regeneration. The researchers hope that these cells could one day be used for clinical treatments of a wide range of medical conditions as the discovery may help scientists create better and safer tissues for use in regenerative medicine. It also will allow scientists to better understand the differences between pluripotent stem cells, which can become every cell in the body, and cells that have lost their pluripotency and are on their way to becoming specific types of tissue cells.

Scientific Abstract:
Our understanding of how mesodermal tissue is formed has been limited by the absence of specific and reliable markers of early mesoderm commitment. We report that mesoderm commitment from human embryonic stem cells (hESCs) is initiated by epithelial-to-mesenchymal transition (EMT) as shown by gene expression profiling and by reciprocal changes in expression of the cell surface proteins, EpCAM/CD326 and NCAM/CD56. Molecular and functional assays reveal that the earliest CD326-CD56+ cells, generated from hESCs in the presence of activin A, BMP4, VEGF, and FGF2, represent a multipotent mesoderm-committed progenitor population. CD326-CD56+ progenitors are unique in their ability to generate all mesodermal lineages including hematopoietic, endothelial, mesenchymal (bone, cartilage, fat, fibroblast), smooth muscle, and cardiomyocytes, while lacking the pluripotency of hESCs. CD326-CD56+ cells are the precursors of previously reported, more lineage-restricted mesodermal progenitors. These findings present a unique approach to study how germ layer specification is regulated and offer a promising target for tissue engineering.

PNAS Lens Free Article Link: